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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 03/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/855,320	BAYER, ROBERT	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8,10-17,19-36,38,40,42-49,51-55,66-68,70-77 and 79-106* is/are pending in the application.

4a) Of the above claim(s) *22-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,8,10-17,19-21,31-36,38,40,42-49,51-55,66-68,70-77 and 79-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The previous Office action was inadvertently indicated as Final rejection on the Office Action Summary-FORM PTOL-326. The previous Office action was a non-final rejection. However, the instant Office action has been made final.

Claims 1-4, 6, 8, 10-17, 19-36, 38, 40, 42-49, 51-55, 66-68, 70-77, 79-106 are currently pending and are present for examination. Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-55, 66-68, 70-77, 79-106 are now under consideration. Claims 22-30 remain withdrawn from consideration as being drawn to non-elected invention.

Applicants' amendments and arguments filed on 12-9-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically Examiner has withdrawn the rejections under 35 U.S.C. 112, 1st paragraph in view of the persuasive arguments presented by the applicant.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-52, 66-68, 70-77, 79-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seed et al. (WO 96/40881, 12-19-1996), de Vries et al. (J. Biol. Chem., 1995, Vol. 270 (15:8712-8722) or Malissard et al.

(BBRC, Jan 2000, Vol. 267:169-173), and Paulson et al. (WO 98/31826, 7-23-1998). Claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-52, 66-68, 70-77, 79-86 of the instant application are drawn to a method of modifying glycosylation pattern of a glycopeptide or a recombinant glycopeptide comprising an acceptor moiety comprising contacting the glycopeptide with a reaction mixture containing fucose donor moiety and a fucosyltransferase under appropriate conditions to transfer fucose from the donor to acceptor such that the glycopeptide has a substantially uniform fucosylation pattern or wherein 80% of the acceptor moieties are fucosylated and wherein the fucosyltransferase is from a eukaryotic source and lacks a membrane anchoring domain and is recombinantly produced, and wherein the glycopeptide is a full length peptide or is an enzyme, cytokine etc. or wherein the glycopeptide is on a cell, wherein the donor is a GDP-fucose. The method also encompasses use of immobilized support and affinity chromatography (claims 1, 8, 10-11, 12-17, 19-21, 31-33, 40, 42-50, 52-53, 70-74, 82-86) and either successive fucosylation by a first and a second fucosyltransferase or a simultaneous fucosylation using two fucosyltransferase (claims 3-4, 6, 34-36, 38, 66-68, 75-77, 79-81). The method also comprises a first glycosylation using a glycosyltransferase other than FT such as a sialyltransferase or a glycosyltransferase followed by fucosylation using a FT.

The reference of Seed et al. provides sources for fucosyltransferases such as FucT-IV and FucT-VII (see page 2) and provides the background information regarding fucosyltransferases and their ability to fucosylate glycopeptides and glycolipids. While the reference teaches the fucosylation of acceptor moieties, it does not specifically teach that 80% of the acceptor moieties are fucosylated. At the same time the reference does not also say that less than 80% of the

moieties were fucosylated as well. The reference also does not teach the that the fucosyltransferase enzyme lacks membrane anchor domain.

Malissard et al. and de Vries et al. teach the process of making soluble fucosyltransferase enzyme which lack their membrane anchoring domain. The reference of Mallissard et al. teaches a method of making the fucosyltransferase-VI as an expressed soluble protein in *Pichia pastoris* host cells by replacing the membrane anchoring domain of the fucosyltransferase enzyme with the N-terminal signal of S.cerevisiae α-factor and demonstrate that the recombinant soluble enzyme had similar kinetic properties as its native counterpart. On similar lines, de Vries et al. also teach the construction of different lengths of human fucosyltransferases and compare the soluble form having a replaced membrane anchoring domain with that of its native counterpart. Here also the reference teaches that the soluble recombinant proteins were more active than their native counterpart.

Paulson et al. teaches methods for *in vitro* sialylation of recombinant glycoproteins. The reference essentially teaches a method of glycosylation involving an enzyme other than a fucosyltransferase.

Combining the teachings of the above references, along with the common knowledge in the art regarding enzyme immobilization and affinity chromatography etc. it would have been obvious to those skilled in the art, to alter the method of fucosylation of a polypeptide as taught by Seed et al. using a soluble recombinant fucosyltransferase such as lacking its membrane anchor domain, as taught by Malissard et al. or de Vries et al. and use such enzymes to modify the glycosylation pattern of a glycopeptide by fucosylating a glycopeptide --either with a single enzyme or with more than one of the above enzymes either by using them simultaneously or

sequentially--, that is already glycosylated (sialylated) as taught by Paulson(b) et al. by incubating the reaction under such conditions and time such that the glycopeptide has substantially uniform fucosylation pattern or wherein 80% of the acceptor moieties are fucosylated. It would be obvious to those skilled in the art to start the reaction with the soluble recombinant enzyme lacking membrane anchoring domain and supplement the reaction using the native form of the enzyme as a second enzyme (as claims in claims 3-4, 6, 34-36, 38, 66-68, 75-77, 79-81). It would be well within the skill of those artisans in the art to extend the incubation time or add extra enzyme (as a second enzyme) or manipulate the immobilized columns such that the resulting glycopeptide is substantially uniformly fucosylated. One of ordinary skill in the art would be motivated to do so as Seed et al. teach that fucosylated proteins produce therapeutics useful for treatment of diseases such as adverse immune reaction. One of ordinary skill in the art would have a reasonable expectation of success since Seed et al. teach almost an identical system but with enzymes which may not lack membrane anchor domain which deficiency is overcome by the reference of Malissard et al. or de Vries et al. which teaches soluble fucosyltransferase fragments lacking their membrane anchor domain can be successfully made and that such enzymes indeed exhibit higher activity. Applicants have agreed in their remarks that once a fucosyltransferase enzyme is made available, one skilled in the art can r4eadily identify the stem region, transmembrane region and the C-terminal region based on the amino acids in those regions and delete such trans-membrane domains for it to be used in the present invention. Also, one of ordinary skill in the art would have a reasonable expectation of success since the fucosyltransferases are readily available in the art, and methods to make them soluble by removing their membrane anchor domain and methods for immobilization of enzymes

and affinity chromatography and methods to determine the amount of fucose groups on a given polypeptide are all well known and available to those skilled in the art.

Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action, applicant has amended the claims and traversed the previous rejection. In view of such amendments, Examiner has combined the previous two rejections into a single rejection using some new references. Applicant appears to focus on the fact that instant claims are drawn to the use of fucosyltransferases lacking membrane anchor domain in vitro and that the combination of previous references provided by the Examiner did not teach or suggest the same and in fact, the reference of Natsuka et al. taught away from the reference because it taught that enzymes lacking membrane anchoring domain cannot be expressed or obtained from transformed cell lines. Without acquiescing to applicant's argument, Examiner has removed the references of Natsuka et al. as well as that of Costa et al. from the rejection.

It is agreed that instant claims (some claims) are now limited the use of eukaryotic fucosyltransferase lacking membrane anchor domain in a *in vitro* condition. However, as stated in earlier Office actions, and reiterated here it is also well known that transferases which are normally membrane bound and have solubility problems and therefor are not suitable for process involving immobilization etc. It is also well known in the art that such problems can be solved by removing membrane spanning domains which renders the enzyme soluble and thereby increases the efficiency of the enzymatic reaction. The above recited references provides evidence to such a conclusion.

Next applicant argues that cited references fail to teach all the claimed elements. Examiner respectfully disagrees with such an argument. Again, Examiner reminds applicant that the above rejection is an obvious rejection and it is the combination of teachings that render the invention obvious. Applicants refer to Paulson reference and argue that it does not discuss fucosylation. Examiner reiterates that said reference was included in the rejection to show the availability of method to glycosylate peptides using enzymes other than FT was well known in the art. This reference was used in order to address claim limitations such as glycosylation by an enzyme other than an FT.

Therefore, contrary to applicant's argument the above rejection is maintained.

Claims 54-55, 87-106, are rejected under 35 U.S.C. 103(a) as being unpatentable over Seed et al. (WO 96/40881, 12-19-1996), de Vries et al. (J. Biol. Chem., 1995, Vol. 270 (15:8712-8722) or Malissard et al. (BBRC, Jan 2000, Vol. 267:169-173), and Paulson et al. (WO 98/31826, 7-23-1998). Claims 54-55, 87-106, of the instant application are drawn to a large-scale method of modifying glycosylation pattern of a glycopeptide comprising an acceptor moiety or producing a recombinant glycopeptide having a fucosylation pattern that is substantially identical to a fucosylated glycopeptide having a known fucosylation pattern comprising contacting at least 500 mg of glycopeptide with a reaction mixture containing fucose donor moiety and a fucosyltransferase under appropriate conditions to transfer fucose from the donor to acceptor such that the glycopeptide has a substantially uniform fucosylation pattern and terminating the reaction when the fucosylation pattern is obtained.

Using the teachings of the above references, along with the common knowledge in the art regarding enzyme immobilization and affinity chromatography etc. it would have been obvious to those skilled in the art, to scale up the method taught by the above two references using different enzymes by employing extra quantities of enzyme or lengthening the incubation times of the reaction. It would be well within the skills of those artisans in the art to extend the incubation time or add extra enzyme or manipulate the immobilized columns such that the resulting method could be set up for large-scale synthesis. One of ordinary skill in the art would be motivated to do so as Seed et al. teach that fucosylated proteins produce therapeutics useful for treatment of diseases such as adverse immune reaction. One of ordinary skill in the art would have a reasonable expectation of success since Seed et al. teach almost an identical systems but not explicitly a large-scale process using full length enzymes.

Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the above rejection, applicant has traversed the above rejection and submits evidence of secondary considerations in support of the traversal. Applicant argues that the *in vitro* method as claimed in the above claims encountered initial expert skepticism but subsequently enjoyed great commercial success, *e.g.,* licensing by others and collaboration with others. Applicant supplies a letter by one such skeptic, Dr. James E. Bailey. However, applicant argues that such skepticisms were overcome and the instant invention enjoyed great commercial success. In support of such success, applicant provides a Declaration from Dr. David Zopf that the present invention was licensed by Wyeth/Ayrest labs and Avant Immunotherapeutics wherein the claimed *in vitro* method provided substantially uniform fucosylation patterns for the

desired glycoproteins on a large commercial scale. Dr. Zopf declares that the instant technology was a success even though Wyeth suspended the development of the glycosylated compound for other reasons unrelated to GlycoAdvance (i.e., instant method). The declaration by Dr. Zopf et al. further indicates that instant invention was successful in glycosylating Avant's complement system inhibitor sCR1-sLe^x and the results of the collaboration study were published in Glycobiology 14(10):883-893. Examiner acknowledges the submission of the above reference. However, a perusal of the reference, specifically, page 890 devoted to "Materials and Methods", does not make it crystal clear that the instant claimed method was indeed used. The reference simply indicates that "rFT-VI (human) was expressed either in NSO cells or in *A.niger* as described as a soluble protein lacking transmembrane domain". However, there is no back-reference to where such description can be found. It is not clear to the Examiner as to which method was adopted for expressing the protein in *A.niger*. In view of the absence of clear documentation that the instant invention was used, it would be hard for those skilled in the art to conclude that the reference provides a clear evidence that the claimed method was used. Therefore Examiner has not given any particular weight to the reference cited in the Declaration as an evidence and continues to maintain the rejection.

Conclusion

None of the claims are allowable.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

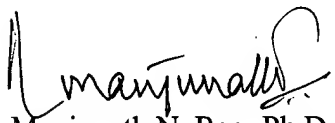
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the

examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

February 21, 2005